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EXPERIENCE OF USING BENZODIAZEPINES IN PREDICTING OUTCOMES AND TARGETED TREATMENT OF PATIENTS IN VEGETATIVE STATE. TREATMENT OF PATIENTS IN VEGETATIVE STATE AND MINIMAL CONSCIOUSNESS STATE WITH ZOLPIDEM (REVIEW)

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ОПЫТ ПРИМЕНЕНИЯ БЕНЗОДИАЗЕПИНОВ С ЦЕЛЬЮ ПРОГНОЗИРОВАНИЯ ИСХОДА И ЛЕЧЕНИЯ ПАЦИЕНТОВ В ВЕГЕТАТИВНОМ СОСТОЯНИИ. ЛЕЧЕНИЕ ПАЦИЕНТОВ В ВЕГЕТАТИВНОМ СОСТОЯНИИ И СОСТОЯНИИ МИНИМАЛЬНОГО СОЗНАНИЯ ЗОЛПИДЕМОМ (ОБЗОР ЛИТЕРАТУРЫ)

С одной стороны, развитие нейрохирургии и реаниматологии создает условия для сохранения жизни той категории больных, которые раньше умирали в первые сутки после черепно-мозговой травмы или других вариантов обширного поражения головного мозга. С другой стороны, мы видим отчетливую тенденцию к увеличению количества больных с тяжелыми вариантами нарушения сознания — вегетативным состоянием (ВС), состоянием «минимального сознания» (СМС). Остается неясным, почему у некоторых больных ВС и СМС могут быть временным этапом, а у других — формой существования в течение многих лет. Описаны случаи отчетливой динамики в виде расширения сознания в ответ на применение золпидема, интратекальной формы баклофена и т. д. у пациентов в ВС и СМС. Данные публикации вызвали широкий интерес у занимающихся этой проблемой исследователей. Почему препараты, которые в обычной ситуации оказывают седативный эффект, у части пациентов в ВС и СМС вызывают парадоксальный эффект в виде «пробуждения»? В статье приведены основные обсуждаемые теории действия ГАМК-ергических препаратов у пациентов в ВС как препаратов, восстанавливающих сознание, а также приведена собственная точка зрения авторов на патофизиологические процессы, лежащие в основе ВС.

Ключевые слова: расстройства сознания, вегетативное состояние, состояние «минимального сознания», ГАМК, золпидем.

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EXPERIENCE OF USING BENZODIAZEPINES IN PREDICTING OUTCOMES AND TARGETED TREATMENT OF PATIENTS IN VEGETATIVE STATE. TREATMENT OF PATIENTS IN VEGETATIVE STATE AND MINIMAL CONSCIOUSNESS STATE WITH ZOLPIDEM (REVIEW)

At present, epidemiology in Russia shows constantly increasing figures of coma survivors in Vegetative State (VS) because of the widespread use of advanced rescue, emergency services, and intensive care treatment with long-term artificial ventilation after acute brain damage.

Cases of recovery from vegetative (VS) and minimally conscious state (MCS) after the administration of various pharmacological agents have been recently reported. The action of CNS depressants as awakening agents sounds paradoxical, as they are commonly prescribed to slow down brain activity. How these drugs may improve the level of consciousness in some brain-injured patients is the subject of intense debate. Some of authors hypothesize that CNS depressants may promote consciousness recovery by reversing a condition of GABA impairment in the injured brain, restoring the normal ratio between synaptic excitation and inhibition, which is the prerequisite for any transition from a resting state to goal-oriented activities (GABA impairment hypothesis). Alternative or complementary mechanisms underlying the improvement of consciousness may include the reversal of a neurodormant state within areas affected by diaschisis (diaschisis hypothesis) and the modulation of an informative overload to the cortex as a consequence of filter failure in the injured brain (informative overload hypothesis).

Key words: disorders of consciousness, vegetative state, minimally conscious state, GABA, zolpidem.

Introdution

Severe brain damage of different nature is often followed by coma — a state in which a person shows the lack of ocular responses, inability to localize noxious stimuli, lack of verbalization. Consciousness is usually recovered alongside the emergence of arousal. Although in some cases wakefulness is not accompanied by any signs of both self- and situational awareness. A conventional term to describe wakefulness without any signs of awareness is *vegetative state* (VS). Currently, the term *vegetative state* applies to complete absence of self- and situational awareness accompanied by preserved sleep-wake cycles with absolute or partial preservation of hypothalamic and brainstem vegetative functions. VS can be diagnosed according to the following criteria, as established by the Multi-Society Task Force on PVS: 1) spontaneous eye opening without evidence of awareness of the environment; (2) no evidence of reproducible voluntary behavioural responses to any stimuli; (3) no evidence of language comprehension or expression; (4) intermittent wakefulness and behaviourally assessed sleepwake cycles; (5) normal cardiorespiratory function and blood pressure control; (6) preserved pupillary, oculocephalic, corneal, and vestibulo-ocular reflexes.

The Vegetative State — a Syndrome in Search of a Name

VS can last range from weeks to years. It is considered persistent if remaining at least one month after the primitive injury. However, the term "persistent" does not imply a condition of irreversibility, as wrongly suggested on some occasions. VS may be defined persistent in the same way as rain when persisting over days: persistent VS may progress to a minimally conscious or a fully consciousness state exactly as prolonged rainfall may suddenly stop. On the other hand, the adjective "permanent" implies a condition of irreversibility, which is mainly deduced by instrumental findings. In fact, although ethical caution suggests avoiding terms referring to irreversibility, sometimes clinical, neuroradiological and neurophysiological findings are so dramatic that there are sufficient data to ascertain that the chances of recovery, if any, are exceedingly small. To avoid confu-

sion between the condition of "persistence" and "permanence" the Royal College of Physicians in the United Kingdom suggested to replace the term "persistent VS' with "continuous"VS. The term *vegetative state* has gained clinical criteria and became an official international term in legal practice and insurance business. So this term can be considered to be generally accepted by the majority of specialists. However, European society for the study of consciousness disorders suggested to replace the term "Vegetative State" with "Unresponsive Wakefulness Syndrome". The authors noted that VS can be both transient (acute) or chronic — among 356 patients with VS 55% of patients were diagnosed with the recovery of consciousness. Due to inhomogeneity of patients in VS and the probability of transient VS after the emergence from coma the authors consider the term "Unresponsive Wakefulness Syndrome" to be more neutral and optimistic rather than "Vegetative State".

Epidemiology of VS in Russia

Until now there have been no statistically based studies on the epidemiology of VS in Russia. We conducted a questionnaire in 15 major hospitals in different regions of Russia. For the 4 years the total number of patients in VS in these clinics was 747 people. The main cause of VS is intracranial injury — 42.57% (318 patients),cerebral infraction resulted in VS — 20.7% (155 patients),cerebral subarachnoid hemorrhage — 17.5 (131 patients), hypoxia — 10.17% (76 patients). Age range was 21–80 years; VS outcome was assessed by the Glasgow outcome scale. Only 4.4% of patients were diagnosed with complete recovery, 17.2% — medium disability (patient is able to take care of themselves), 42.8% — deep disability(patient shows elementary signs of consciousness, but unable to take care of themselves), 22.4% — chronic VS, 9.6% — fatal case. In the last 15 years patients in VS of different nature all across Russia have been admitted to the Neurosurgery. In 2002–2015, the Anesthesiology and IC Department have treated 210 patients with disorders of consciousness (DOC) — MCS, VS, "locked-in" syndrome (Table 1).

The Pathophysiological Basis of Vegetative State

Why some patients recover their consciousness, while others proceed to VS, which is a transitional stage for some patients, and a form of existence without significant chang-

Table 1

Population demographics and diagnosis by Coma Recovery Scale-Revised (on admission)

Parameter	Vegetative state	Minimal conscious state	Locked-in syndrome
N	156	47	7
Mean age	28.5	27.9	22.1
Women	61	11	2
Month since Onset Mean (range)	0	13	0
<1 month since Insult (n)	15	10	1
1–6 month since Insult (n)	108	17	4
6–12 month since Insult (n)	23	5	2
>1 year since Insult (n)	10	2	0
Traumatic Cause (n)	81	42	0
Hypoxia (N)	52	3	0
Another (N)	23	2	6

es over the years for others? Why are timing and consciousness recovery level so different in these patients? Numerous works describing the morphological structures alteration, functional relationships interruption, physiological systems damage and destruction often do not cover the endogenous mechanisms of nervous system, and event chain is not consolidated by general pathophysiological concept.

The Russian school of pathophysiology created a new avenue in studying the etiology and pathogenesis of nervous disorders in the context of functional systems, dominant relations disorders, common pathological processes. The founders of this avenue are I. M. Sechenov, N. E. Vvedensky, A. A. Ukhtomsky, L. A. Orbeli, P. K. Anokhin. Theoretical and experimental bases of such approach to the central nervous system pathology (CNS) in a most clear way are represented in works of Academician G. N. Kryzhanovsky (1997). By definition of G. N. Kryzhanovsky, common pathological processes in the nervous system are those processes which do not have specific etiologic features, occur in case of various nervous system pathology forms and act as basic mechanisms of pathogenetic nerve disorders.

These processes of neuronal depolarization, aggressive reduction of neuronal excitability and seizure threshold with the increased convulsive readiness, hypersensitivity of the effector neuronal systems that are typical of early postresuscitative period, are the components of common pathological processes known as inhibitory deficits, disinhibition deafferentiation with increased sensitivity of the correspondent brain structures to biologically active substances (Cannon–Rosenbluth's Law), etc. These processes (on a par with primary damage of an organic defect origin) lead to pathological changes of the integrative activity of the nervous system. Necrobiotic processes and ischemia lead to neuronal deafferentiation, along with the increase in their excitability, interruption of their inhibitory tracks, which is one of the mechanisms for the pathologically enhanced excitation generator (PEEG) to come into being. PEEG is an hyperactive neuronal ensemble that produces excessive and uncontrolled flow of impulses, as well as a new and unusual type of pathological interneuronal integration. PEEG can be formed in almost all areas of the CNS, its formation and activities constitute common pathological processes. Thus, the formation of the generator in the caudal part of both caudate nucleus causes parkinsonism symptoms, formation in somnogenic area causes abnormally prolonged sleep. Some non-epileptic paroxysmal states are caused by activities of PEEG (absence seizures, catalepsy). If PEEG is built up in those parts which normally inhibit the activity of other CNS parts, or in parts activating the inhibitory structures, the pathologically enhanced inhibition produced by the generator may result the loss of function. Academician G. N. Kryzhanovsky believes that a profound inhibition of brain structures and synaptic transmission interruption contribute to consciousness and certain brain functions loss in case of posthypoxic encephalopathy (Kryzhanovskiy G. N., 1980).

It can be assumed that in VS patients — alongside their regular sanogenetic flexible processes — another process takes place. The formation of a new pathological information integration pattern and the formation of pathological systems in the nervous system, which maintain the brain in a state that can be clinically characterized as vegetative. The collapse of the pathological system, sanogenetic processes implementation underlie consciousness recovery and the emergence from VS.

The picture of a "diver", presented below, was found during the excavations of the ancient Italian city Paestum (Fig. 1). It is believed that it depicts a young person making a leap into the unknown, into the void.

We used this allegory for patients in vegetative state who are "stuck" in their leap between the existence and the void. VS, in our view, is a new variant of organizing functionality that may be entitled as allostasis. On the one hand, this variant of the brain function organization shows processes that are not specific for homeostasis: disautonomia, hormonal disorders, character of relationship between macroorganism and pathogenic and opportunistic pathogenic microorganisms. On the other hand, mentioned sur-

Fig. 1. Picture "diver", found during excavations in Paestum:
a leap into the unknown, into the void

vey results indicate the absence of focal neurological symptoms that are specific only for patients in VS, changes in brain metabolism as well as brain structural changes, illustrated by modern neuroimaging techniques. According to the concept of the ergotropic and trophotropic states by the Swiss physiologist W. Hess (W. Hess, Nobel Prize in Medicine, 1949) — VS is an ergotropic state. All patients had accented adrenergic reactions in common (dysautonomia): tachycardia, periodic blood pressure increase, predominance of sympathicotonia according to cardiointervalography. We didn't find a distinct correlation between the observed functional disorders in patients in VS and the results of different neuroimaging examinations methods.

It turns out that quite complex examinations of patients in VS cannot explain the reason why some patients regain consciousness sooner or later, and some of them remain in the VS until the end of their life? It remains unclear which clinical data should be considered in these patients by outcome predicting the pathogenetic therapy appointment.

For the basis for the search of answers to these questions we accepted a hypothesis that VS in some patients is a consequence of a stable pathologic system formation, that limits the brain functional activity. Identification of such a system may allow to forecast consciousness recovery possibility because functional disorders are not fatal, while they are typically in case of CNS morphological changes. Suppression of a stable pathologic system activity can be the basis of pathogenetic therapy for patients inVS. Spontaneous EEG registration under benzodiazepine-induced pharmacological stress has become the primary method of a stable pathologic system activity identifying in patients in VS

EEG Pattern Examination under the Conditions of Benzodiazepine-Induced Pharmacologic Stress

Selecting of the testing study medication was based on the fact that benzodiazepine receptors are part of the GABAergic system, which is one of the main "inhibitory" systems of the brain. This system provides a balance between excitation and inhibition in the CNS and plays consequently an important role in stable pathological systems activity suppressing in a number of CNS disorders. Also the basis for benzodiazepines selection was the presence of their direct antagonist — Flumazenil (Anexate). Its usage has allowed to study the causal relationship between the administration of the drug and its effects more reliably.

After EEG registration for patients complying with VS diagnosis, a pharmacological test with benzodiazepines was conducted. The drug of choice was midazolam. The drug was administered at a rate of 0.04 mg/kg. 3–4 min after administration, EEG was recorded for 5 min. In case of restructuring absence, the drug was repeated in the same dosage, after 3–4 minutes the EEG was re-recorded, and the procedure was repeated till the advent of EEG restructuring or to a maximum dose of 15 mg of midazolam. The test was considered to be positive if after injection of intravenous benzodiazepines, EEG pattern restructuring was observed. We have observed a slight correlation between baseline EEG patterns and the nature of its restructuring against the background of benzodiazepines administration. Thus, the low-amplitude EEG activity was rebuilt with the advent of alpha- and beta-spectrum. In patients with slow-wave activity of theta- and delta — spectrum appeared stable fast forms, and in patients with baseline polymorphic bioelectric activity pattern, there was a prevalence of alpha activity (Fig 2, 3).

In order to confirm the correlation between the benzodiazepine drugs effect and EEG pattern restructuring, a competitive antagonist of benzodiazepines — Flumazenil (Anexate) was administrated at a rate of 0.1 mg every 1 to 2 minutes until the original EEG pattern was registered again.

If the administration of Flumazenil restored the original EEG pattern, it was considered that the reason of brain activity restructuring with the emergence of new forms of activity is benzodiazepine. The initial EEG pattern was apparently a reflection of a stable pathologic system functional activity. We have not observed spontaneous EEG rearrangements, that were not connected to the benzodiazepine administration.

The test was considered to be negative if after a maximum dose of benzodiazepines no EEG pattern reconstructions occurred.

In our opinion, appearance of a brain activity close to "normal" brain activity against the background of benzodiazepines administration showed the presence of a functional component in the VS structure and confirmed the correctness of the study underlying hypothesis. The next task was to fix the brain functioning level, identified during the test in order to create the conditions for the complete pathological system suppression.

Determination of the Dose and Frequency of Benzodiazepines Administration in Order to Create Conditions for Suppression of a Stable Pathological System Activity

For patients whose test results were positive, the minimal dose of the drug that caused the most distinct changes in the EEG was selected. After the determination of a minimal single dose, the daily dose and frequency of administration was calculated. Taken into account the half-life of midazolam, the minimal single dose during twenty-four hours was administered every 4 hours. Studies have shown that doses of benzodiazepines, required to obtain EEG pattern reorganization, are different. They do not depend on the original pattern and presumably reflect the individual ratio of inhibitory and excitatory processes in each patient.

Determination of benzodiazepine doses required 48–72 hours. An EEG was recorded one or two times a day during this period. The criterion of appropriate benzodiazepine dose was the preservation of EEG pattern, obtained after administration of a benzodiazepine minimal single dose.

As mentioned above, all the patients showed dysautonomia symptoms: greasiness of the skin, increased body temperature with isothermia (difference between the skin temperature and temperature in the rectum was less than 0.5 °C), tachycardia, increased blood pressure. Clinical signs of dysautonomia in most patients proceeded against the background of a stable EEG pattern, formed by the benzodiazepine administration. In some patients, dysautonomia symptoms(tachycardia, increased blood pressure, greasiness, hyperthermia with isothermia) were accompanied by the emergence of hypersynchronized

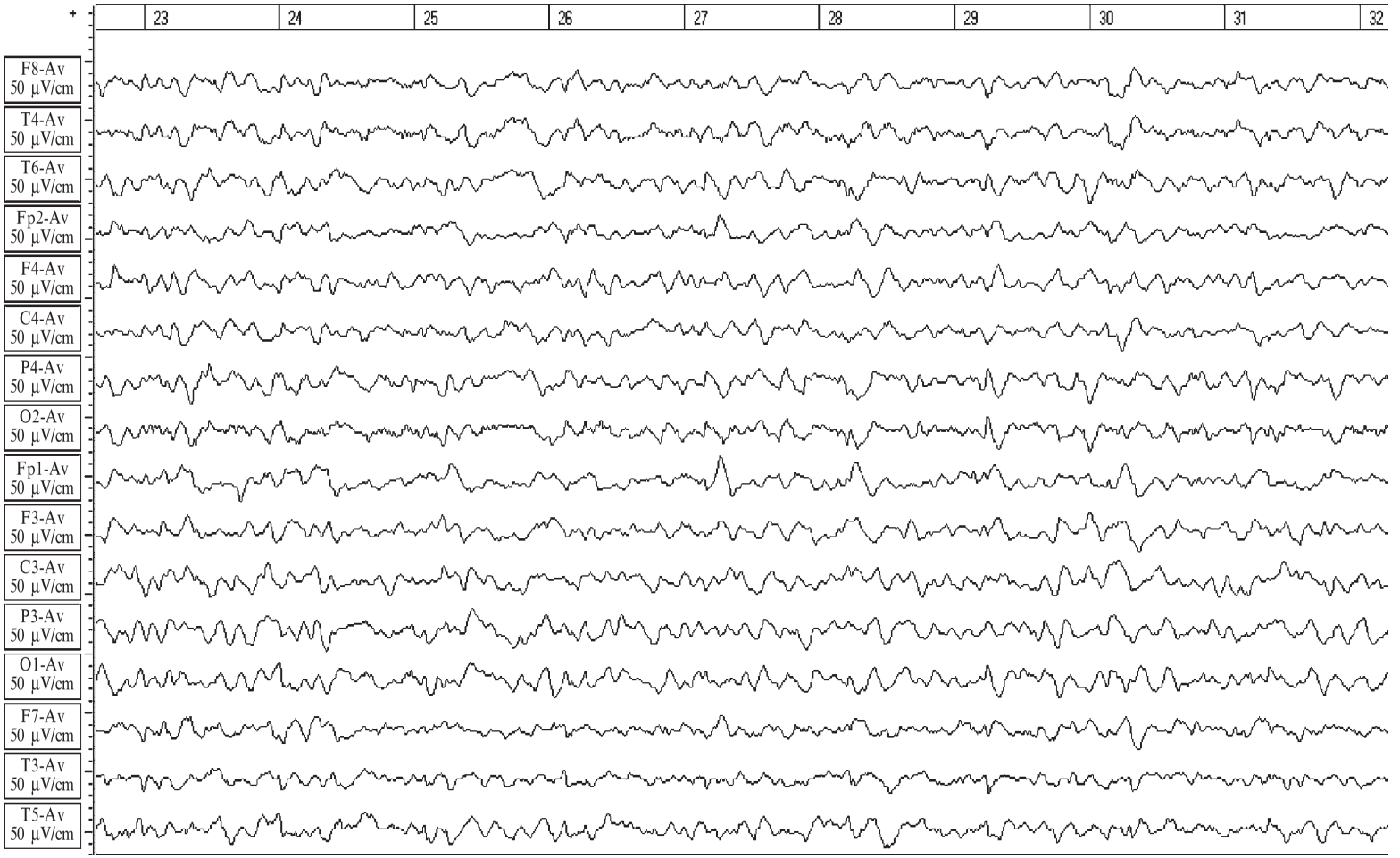

Fig. 2. Patient A., 33 years old, traumatic VS for 5 weeks. Initial EEG, low-amplitude EEG activity

Fig 3. EEG restructuring of the initial EEG pattern after 5 mg diazepam i/v.
The low-amplitude EEG activity was rebuilt with the advent of alpha- and beta- spectrum

activity in the theta- and delta-spectrum, and that required dose adjustment of benzodiazepine.

Against the background of the twenty-four-hour benzodiazepine administration in dosages providing preservation of EEG pattern, that is closer to the "normal" one, the following changes in the patient's condition were observed. First of all, there was a clear correlation of wakefulness periods with time of day, which in our opinion is an evidence of one of the most important CNS biorhythm normalization. Patients spent most of the daylight hours with open eyes. We also saw a so-called "limbic emotional reaction" — in other words, mimic emotional expression equivalents on various stimulations, including noxious stimulus, that are not accompanied by signs of self- and environmental consciousness. Also, periodic changes in muscle tone became distinct 2–3 times a day, the tone increased, then decreased. During this period, the EEG recorded a bioelectrical activity pattern, similar to the one received during the previously conducted test with benzodiazepines. Thus, we can say that on the background of the twenty-four-hour benzodiazepine administration, at first glance paradoxical reaction to this drug was observed — activation of the functional activity of the brain.

The received data confirmed the correctness of the hypothesis that a stable pathologic system limits the activity of the brain in patients in VS greatly, and most importantly — that it is possible to selectively suppress the activity of this system with the simultaneous normal brain function activation.

The first signs of consciousness in patients appeared after 4–5 weeks of benzodiazepine administration. These characteristics primarily were staring and tracking of moving objects with the eyes. Against the background of these consciousness demonstrations, patients began to follow simple orders. Mimic emotional reaction demonstrations became more differentiated. Almost simultaneously with the first signs of consciousness recovery was the changing EEG pattern: in some patients appeared an alpha rhythm, in the remaining cases, there appeared a stable beta-, alpha-spectrum activity.

Thus, the suppression of the pathological stable system restores the brain functional activity to a level of minimally consciousness state. Naturally, there are questions: how stable is the functional state obtained using benzodiazepine? What can be considered a criterion for discontinuation of these drugs administration? We can obtain answers to these questions using the technique "diagnostic window".

Defining the Reasonability of Further Benzodiazepine Use after the Signs of Consciousness Appearance

In order to reduce the benzodiazepine dose after the first signs of consciousness, showing the patient transition into minimal consciousness state, a "diagnostic window" was observed.

The following "diagnostic window" procedure was developed. As the main criterion for the stable pathologic system suppression in our research has been a closest to "normal" EEG pattern, it was decided that the basis for stability determining of state obtained with benzodiazepines administration should be, above all, EEG. The benzodiazepine administration was stopped 6 hours prior to EEG recording. This interval overlaps one half-life of the drugs we used, and EEG recorded after such an interval can be considered to be spontaneous and independent of the benzodiazepine effects.

EEG patterns redevelopment observed against the benzodiazepine administration background confirm that there is a morpho-functional capacity to support the electrobiological activity that is significantly closer to the normal standards than recorded previously. Pharmacological maintaining of this activity level after a while is accompanied by a significant improvement of the patient's neurological status, even up to consciousness recovery.

According to modern CNS pathophysiology ideas, our proposed diagnostic and treatment method is a method of stable pathologic system activity suppression. Most likely, benzodiazepines are not the only group of drugs suitable for this purpose, because the

problem of CNS inhibitory and excitatory processes is complex and ambiguous. In certain situations, stimulating drugs have clear "inhibitory" effects and vice versa. Apparently, benzodiazepines are the drugs of first choice in the treatment of VS patients.

The main result of this study should be regarded that patients, in whom clear EEG pattern reorganization during the pharmacological test was observed, later recovered consciousness. Those patients who did not have these reorganizations, remained in VS for the whole period of observation. In our opinion, this is a clear proof that some patients in VS, the absence of consciousness is caused by an active stable pathologic system (the temporary dominance). In cases without such a stable system activation, the unconsciousness phenomenon, considering the non-specificity of all other signs, is possibly caused by anatomical thalamocortical connection destruction.

Spontaneous consciousness recovery in patients as seen, for example, using Zolpidem is likely due to pathological stable system destruction, because functional states have no clear sanogenesis temporal characteristics.

Zolpidem in the Treatment of Patients in the Vegetative State

There are no evidence-based recommendations regarding pharmacological treatments capable of improving the level of consciousness in DOC patients (Demertzi et al., 2008). zolpidem has been reported as an "awakening drug" in some patients suffering from disorders of consciousness (M. Thonnard, 2013). Whereas zolpidem, an imidazopyridine, is generally used as a sedative-hypnotic drug, it seems that it occasionally produces, temporarily, a surprising paradoxical effect on the level of consciousness in some DOC patients, irrespective of whether they have a traumatic or non-traumatic etiology (Gosseries et al., 2013). The numerous case reports present in the literature may result in overestimation of the rate of patients in whom zolpidem works as a "waking up pill". A wide range of behavioral improvements have been reported including the emergence of visual pursuit, command following, verbalizations, functional communication, motor improvements (e. g., ability to walk) and/or cognitive (e. g., reading, counting, writing) improvements (Brefel-Courbon et al., 2007; Clauss and Nel, 2006; Clauss et al., 2000; Cohen and Duong, 2008; Shames and Ring, 2008; Whyte and Myers, 2009). However, the proportion of DOC patients in whom zolpidem produces such an effect is not well documented. Despite the existence of numerous case reports about zolpidem in DOC, only Whyte and Myers (2009) have investigated the incidence of responders among DOC patients. In their study, only one out of 15 patients evolved from VS to MCS (6.7% responder rate) and demonstrated behavioral improvements, namely visual pursuit and response to command.

In 2000, Clauss et al. reported an interesting case of the paradoxical positive effects of zolpidem in a "semi-comatose" chronic TBI patient. Upon administering 10 mg in order to reduce the patient's agitation, very much to their surprise they observed the patient "wake up", which manifested in him greeting his mother and in providing appropriate answers to a series of questions about him and his environment for the first time since his accident three years before. The researchers also provided assisting support to these behavioral and cognitive improvements by demonstrating the EEG activity in response to eye opening. At the same time, the brain single-photon emission computed tomography (SPECT) showed a substantial increase in the thalamic, the lentiform and the caudate nuclei activity. The patient's peak of responsiveness was observed about an hour after the administration of the drug and lasted for a maximum of four hours. In light of such cognitive functioning improvement with the course of time, this team later published a longitudinal zolpidem trial which followed up three chronic patients in VS for three to six years to further evaluate the drug's efficacy over time. They reported that the drug did not lose its efficacy, and the patients progressively improved since the first day of treatment if assessed with the GCS and RLA cognitive scale. These positive changes were found significant because the patients (previously considered unconscious) could respond to simple commands, interact with their environment, eat independently, watch

television, and show appropriate emotional responses. Moreover, no deleterious side effects could be observed in the patients after three to six years of daily 10 mg doses. In line with the first case study, it was found that the response peak was observed one hour after the administration, and the patients returned repeatedly to VS after a maximum of four hours.

The efficacy trials of zolpidem have shown that the VS group is heterogeneous, including in the way the patients respond to drug stimulation of the brain. Quite a few studies have failed to confirm any kind of pronounced effects of zolpidem in patients with VS or reduced consciousness.

Shyman et al. performed the first pediatric prospective, double-blind, placebo controlled randomized trial in three VS children, resulting in controversial findings. The clinical trial consisted of two four-day treatment intervals alternated with a 10-day washout period when the children received either daily doses of zolpidem of 0.14 to 0.20 mg/kg or placebo. Clinical outcomes were measured with the RLA and the CNC scales as well as with the use of FDG-PET. They reported no change in the RLA scores after the administration of the drug, while there was an increase in the CNC scores, suggesting a sedative effect consistent with the normal effect of the drug. The study of spontaneous brain metabolic activity showed no changes after zolpidem treatment.

An open-label study (M. Thonnard et al.) failed to show any clinically significant improvement (i. e., change of diagnosis) in any of the 60 studied chronic DOC patients. M. Thonnard et al. presented the results of a rospective open label study in chronic DOC patients. Sixty patients with a diagnosis of VS (n=28) or MCS (n=32) were behaviorally assessed using the Coma Recovery Scale-Revised (CRS-R) before and one hour after administration of 10 mg of zolpidem. At the group level, the diagnosis did not change after the administration of zolpidem while the CRS-R total score decreased. Twelve patients (20%) showed improved behaviors and/or CRS-R total scores after zolpidem administration, however, the diagnosis after the administration of zolpidem significantly improved only in one patient (functional object use test), which suggested a change of diagnosis. A double-blind placebo-controlled trial was performed in this patient in order to better specify the effects of zolpidem, but the patient, on this trial, failed to show any clinical improvements.

Many authors agree on that zolpidem has ambiguous effects. The level of interaction did not improve in a proportion of patients after the drug administration. Recent publications underline the importance of dose titration in order to obtain maximum effects of the treatment.

Adam Wysokinki et al. (2014) used a higher dose of zolpidem (30 mg) to evaluate whether the drug's response could be dose-dependent. Indeed, patient's improvement was strictly related to the increase in zolpidem dosage, with a relatively good response at 30 mg. The authors do not seem to provide a plausible explanation of this interesting finding, although a more pronounced effect that high-dose zolpidem may exert on the centrothalamic activity (by potentiating the "mesocircuit"), could be viewed as a probable explanation.

The mechanism by which zolpidem is able to transiently restore neurological functions is still unknown. Literature on the subject most often refers to the following putative mechanism. The spectacular effects of zolpidem have also been attributed to the stimulation of sleeping brain regions. In fact, the mechanism of neuronal dormancy was introduced to explain the effects of zolpidem: certain nonspecific areas of the brain, adjacent or distant to the initially damaged zone (e. g., the ipsilateral, contralateral hemisphere, or cerebellum) can be inhibited after the brain insult. During the acute phase, the neuroprotective dormancy mechanism enhances the release of GABA in order to reduce and suppress the activity of the brain, and to prevent excitotoxicity in order to facilitate the recovery of the brain tissue or to prevent greater neuronal loss. Transient recovery of consciousness would be mediated by a selective omega-1GABA-agonistic action in re-

versal of that neuronal dormancy observed soon after the brain injury. When the patient enters the chronic phase, GABA levels will go back to normal or slightly decrease, but the neuroprotective GABA mechanism can still be the reason why the functional activity of critical brain regions fails to restore the consciousness.

Another view is that inconsistency and the rarity of the effects could therefore be explained by the high specific action of the substance on viable dormant brain regions and thus, in cases of more extensive brain injuries, zolpidem as well as other pharmacological treatments would not produce therapeutic effects. The authors advocate one more remarkable theory which attributes restored arousal, and cognitive functionality to the probable ability of zolpidem to restore neuronal desynchronization. After severe brain damage, the neuronal activity loses its power of complex information integration (resulting from desynsynchronization among neuronal population) and enters a state of homogeneous synchronization. This increasing pathological synchronization is observed with the presence of slow wave activity across the cortex, and is associated with cognitive decline and a neuropathologically altered state of consciousness. Desynsynchronization among neuronalpopulation — probably results from neuronal depolarization in the acute phase, the decrease in the neuronal excitability threshold with increased convulsion threshold and hypersensitivity of the neuronal effectory systems. All the described phenomens are part of a common pathological processes: inhibitory deficit, disinhibition and deafferentiation with enhanced sensitivity of the structures of the brain to biologically active substances (Cannon Rosenbloth Law, etc.). Alongside the primary organic lesion, these processes cause a pathological disruption of the integrative activity of the nervous system and contribute to the formation of pathologically enhanced excitation generators (PEEG).

We opine that desynchronization among neuronal population and increasing pathological synchronizations is a variant of PEEG, which maintains the complete suppression of cognitive functionality of the brain resulting in VS. The quick effects of zolpidem that develop within the first hour following its administration have to do with the suppression of PEEG and temporary disruption of the stable pathological pattern. Due to the effects they exert on the major inhibitory systems of the brain, GABA drugs seem to be the most appropriate candidates. The VS patients, therefore, are a heterogeneous group demonstrating variable and sustainable brain pathology, these people demonstrating the "sleeping beauty" type of awakening manifested by quick and spectacular regaining of consciousness upon the administration of certain drugs (zolpidem, dopaminergics, intrathecal administration of baclofen).

It is likely that zolpidem promotes the reactivation of "dormant" neural networks because, when it binds allosterically to modified GABA receptors in neurodormant cells, the receptor conformation is altered and, subsequently, the promulgation of abnormal cell metabolism terminates. Several single-photon emission computed tomography (SPECT) studies (Cohen L et al., 2008, Clauss RP et al., 2004) have suggested that zolpidem is able to reverse diaschisis, which is a condition of depression of regional neuronal metabolism and cerebral blood flow in brain areas that are anatomically distant but functionally related to the damaged neuronal region. Indeed, zolpidem induces a marked increase in blood flow within those areas of the brain that are adjacent to or distant from the damaged tissue. Moreover, in the 'mesocircuit' model proposed by N. Schiff et al. 2010, zolpidem could directly inhibit the globus pallidus internus, where the GABA(A) subunit is expressed in large quantities, leading to a more normal level of central thalamic activity. The improvement of clinical symptoms that has been observed after zolpidem depends on the severity of brain damage and on the size and location of the dormant brain site. A recent SPECT study by Du et al. (2013) showed good efficacy of zolpidem in VS patients after brain injury, especially in those whose brain damage was in non-brainstem areas. The authors suggested that slight damage to non-brainstem areas may lead to a condition of "brain dormancy" rather than cellular apoptosis. Conversely, severe brainstem injury may lead to an apoptotic process and cell death, resulting in irre-

versible disruption of important functional areas. This implies the presence of neuronal systems that are dysfunctional but are not permanently destroyed and thus are subject to pharmacologic reactivation. This could be the reason why zolpidem is not effective in all patients with DOCs, as seen in some cases. In addition, zolpidem had no beneficial effect in an MCS patient, suggesting that when the damage is severe, even a condition with a higher functional level may not benefit from its administration (R. Singh, et al. 2008). Several of the reported successes with zolpidem have been after hypoxic-ischemic injuries (C. Tucker, K. Sandhu, 2015). Its use could be reasonable in select patients with neurologic injury but promising integrity of brain structures, such as intact deep and superficial gray matter structures and white matter connections. Tucker and Sandhu note that increased arousal has been observed in both traumatic and non-traumatic brain injury; however, patients with NTBI demonstrate more of the arousal effects than TBI patients (Tucker, K. Sandhu, 2015).

According to the hypothesis of F. Pistoia et al. (2014), CNS depressants might partially reverse a condition of impaired cortical GABA neurotransmission, which hinders functional synchronization in the injured brain. F. Pistoia et al. hypothesized therefore, that patients with DOC show impaired GABA modulation and that CNS depressants may facilitate an improvement in the level of consciousness by restoring the brain interconnectivity and a balanced level of inhibition during transition from rest to computational states. This hypothesis is also in line with the findings of a double-blind, randomized, placebo-controlled, cross-over study showing, in healthy subjects, an increase of functional connectivity in the human cortex following the administration of lorazepam, a benzodiazepine hypnotic drug that binds to the GABA(A) receptors (A. Fingelkurts et al. 2004). This additional evidence confirms that GABA-induced inhibition is an active process which, through interaction with specific synaptic and diffuse extrasynaptic GABA receptors, may enhance brain synchronization (A. Fingelkurts et al., 2004).

The diaschisis hypothesis which explains the zolpidem mode of action is close to the theory of stable functional state. Based on this hypothesis, adaptation, which probably develops as a mechanism to contrast hypoxia, leads to a condition of cell dormancy or diaschisis in brain areas which are functionally connected with the damaged one (R. Clauss, 2004) The duration of diaschisis, before it eventually wears off, is variable and may be influenced by factors such as the brain areas involved, the patient's age and comorbidities. According to von Monakow's original theory, diaschisis may also persist indefinitely, without undergoing dissipation over time (S. Finger, 2004). Diaschisis may be more persistent in the presence of interactive factors such as vascular disorders which can interfere with the recovery of distant brain areas. The concept of diaschisis may contribute to explain why some brain injured patients show more severe and diffuse symptoms than is expected on the basis of the initial damage (F. Pistoia et al. 2014). Similarly, the wearing off of diaschisis may be a reasonable explanation for a delayed recovery of functions in the same patients. Diaschisis may also be involved in the functional breakdown of interconnected areas which is associated with DOC. The phenomenon of diaschisis, through a splitting off of these previously interconnected units, may play a significant role in the pathological process leading to the breakdown of consciousness. In these circumstances, DOC may persist until diaschisis is reversed, or may last indefinitely if the interconnectivity is not restored. The diaschisis hypothesis allows to speculate about the mechanisms by which zolpidem, a short acting non-benzodiazepine hypnotic of the imidazopyridine class that binds to the GABA(A) receptors, may exert its effects and enhance the level of consciousness in some brain injured patients with a diagnosis of VS (F. Pistoia et al., 2014) It can be hypothesized that zolpidem exerts its effects by binding to the modified GABA(A) receptors of neurodormant cells within areas affected by diaschisis, thus promoting the reversal of metabolic inhibition (R. Clauss, 2004). In other words, diaschisis is just one of the ways for the determinant system of the CNS to form. The determinant system concept was proposed by the Russian neurophysiologist acade-

mician Kryzhanovsky. This concept is very much unlike the concept of Dominant by Ukhtomsky. The Dominant suppresses the activity of related structures, unlike the determinant, which activates these by remodelling their activity and imposing its proper mode of action. The determinant, therefore, is a type of brain structure that is capable to determine a particular pattern of other parts of the CNS, as well as the overall activity of the system and the results of such activity. In case the determinant structure is hyperactive, equally active is the pathological system it produces. The latter spins out of control and disrupts the integrative activity of the brain. Zolpidem probably suppresses the activity of PEEG responsible for the determinant activity. PEEG is a neurophysiological basis of the determinant. Against the backdrop of this concept we offer another approach to explain arousing Zolpidem effect. At the heart of brain proceedings is "switch on-switch of" rule. We suppose that patients in VS are in "switch on" mode. But brain operation is inefficient in consequence of inner hindrances, likewise radio interference make it impossible listen to the radio. In such circumstances good decision is to switch to another wave. We have reason to believe that method "switch to another wave" may be promising for VS patients.

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